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10/578,521	05/08/2006	Jong-Yoon Chun	50413/015001	7873

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EXAMINER	
PANDE, SUCHIRA	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/578,521	CHUN, JONG-YOON	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-29* is/are pending in the application.

4a) Of the above claim(s) *8,12,17 and 23-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-11,13-16 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Amendment filed on April 1, 2009 is acknowledged. Applicant has amended claims 1, 7, 14, 18-22; withdrawn claims 8, 12, 17, 23-29; and cancelled claims 6 and 30. Currently claims 1-5, 7, 9-11, 13-16, 18-22 are active and will be examined in this action.

Claim Interpretation

2. The claims currently under consideration are method claims for amplifying nucleic acids. The claims recite structural limitations of the primers used in the method. No specific template nucleic acid is recited in the claims. In view of this scenario, the limitations wherein specific portions of said primers are substantially complementary to, a template nucleic acid, therefore reads on a method where the claims encompass primers for any conceivable nucleic acid template, whether naturally occurring or man-made, whether known to exist or capable of being synthesized. Any conceivable nucleic acid sequence can be synthesized and engineered in such a way as to produce gDNA, cDNA or mRNA. In this regard, those particular limitations of the claims pertaining to substantial complementarity are met by any primer depending on the template nucleic acid. Since no specific template is recited in the claims, limitations based on hybridization to random or arbitrary sequence with respect to an unspecified template impart no structural limitation on the claimed primers that are useful in the method, therefore any primer will function in the claimed method.

DNA Walking annealing control primer (DW-ACP) has not been defined, so using broadest reasonable interpretation any primer used in prior art will read upon claim 1 as currently recited.

Response to Arguments

Re 103 rejections of claims 1-5, and 13 over Stone & Wharton as evidenced by Welsh & McClelland in view of Brenner

3. Applicant's arguments with respect to claims 1-5 and 13 have been considered but are moot in view of the new ground(s) of rejection. Applicant has amended base claim 1 to incorporate primer of formula I previously recited in claim 6. In addition Applicant has added a requirement that was not present in original claim 6 namely the regulator portion of claimed primer of formula I comprise at least two contiguous universal base or non-discriminatory base analogs. Both primer of formula I and presence of at least two contiguous universal base or non-discriminatory base analogs is not taught by Stone & Wharton as evidenced by Welsh & McClelland in view of Brenner. Hence previously cited rejection over above cited art is being withdrawn. New art is being cited that teaches all aspects of the amended claim 1.

Re 103 rejections of claims 6-7, 9-11, and 14-22 over Stone & Wharton as evidenced by Welsh & McClelland in view of Brenner as applied to claim 1 above further in view of Liu & Whittier; Watanabe et al. and Oberste et al.

4. Since rejection of claim 1 over Stone & Wharton as evidenced by Welsh & McClelland in view of Brenner is withdrawn hence rejection of claims 6-7, 9-11 and 14-

22 further in view of secondary references cited above is no longer valid and is being withdrawn.

Re 112 rejection of claim 30

5. Claim 30 has been cancelled, thus rendering the rejection of claim 30 moot.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-5, 7, 13-16 and 18-22 are rejected over Stone & Wharton (1994) Nucleic acids Research vol. 22, no 13 pages 2612 -2618—previously cited as evidenced by Welsh & McClelland (1990) Nucleic acids Research vol. 18, no 24 pages 7213-7218—previously cited in view of Brenner (US pat. 5,962,228 issued Oct 5, 1999—previously cited) further in view of Chun (WO 03/050305 A1 published on 19 June 2003 with filing date of 19 September 2002- provided by Applicant in IDS).

Regarding claim 1, Stone & Wharton teach a method for amplifying an unknown nucleotide sequence adjacent to a known nucleotide sequence, which comprises the step of

(a) performing a primary amplification of said unknown nucleotide sequence using a DNA walking annealing control primer (DW-ACP) (see abstract where amplification of cDNA using an arbitrary primer is taught. Arbitrary primer of Stone & Wharton = DNA walking annealing control primer (DW-ACP) of instant claim)

and a first target-specific primer (see abstract of Stone & Wharton where the primer that is member of primer set which corresponds to a conserved region within a specific gene family = the first target specific primer of instant claims); in which said step (a) comprises:

(a-I) performing a first-stage amplification of said unknown nucleotide sequence at a first annealing temperature, comprising at least one cycle of primer annealing, primer extending and denaturing using a first degenerate DW-ACP containing a degenerate random nucleotide sequence to hybridize with said unknown nucleotide sequence and a hybridizing nucleotide sequence substantially complementary to a site on said unknown nucleotide sequence, wherein said first annealing temperature enables said first degenerate DW-ACP to function as a primer, whereby a first degenerate DW-ACP extension product is generated (see last line of page 2612 and beginning of par. 1 on page 2613 where amplification is conducted using both the arbitrary primer as well as primer specific for a conserved region of gene family is taught. The annealing temperature of first cycle is taught as temperature between 40^0C to 50^0C; and

(a-2) performing a second-stage amplification at a second annealing temperature (see page 2613 where second-stage amplification at a second annealing temperature of 50^0C to 60^0C is taught).

Stone & Wharton do not state that at this second annealing temperature the first degenerate DW-ACP ceases to function as a primer. Stone & Wharton have developed the method based on modification of protocol published by Welsh and McClelland (see

abstract). Welsh and McClelland in their 1990 paper (Nucleic acids Research vol. 18, no 24 pages 7213-7218) where they first described arbitrary primed PCR teach the rationale why at higher annealing temperature said first degenerate DW-ACP ceases to function as a primer. They teach cycling at lower temperature for two cycles (annealing at 40^0C)—low stringency annealing followed by amplification under high stringency cycles (annealing at 60^0C) (see page 7214 par. 1). They state "at a sufficiently low temperature, primers (Arbitrary primer PCR primers---note added by Examiner) can be expected to anneal to many sequences with a variety of mismatches". (see results section par. 2 on page 7214). On page 7215 where they determine the effect of temperature on Arbitrary primed PCR they state "The pattern of bands changes slightly as the temperature is raised, until, at some point, the temperature is too high for this set of matches to predominate". The bands were being formed due to annealing of the arbitrary primers to the template and subsequent extensions. In view of this explicit teaching of Welsh and McClelland it is clear that as temperature is increased at some temperature the arbitrary primer ceases to anneal in other words it ceases to function as a primer. Thus Stone & Wharton as evidenced by Welsh and McClelland teach

(a-2) performing a second-stage amplification at a second annealing temperature to render said first degenerate DW-ACP not to function as a primer, comprising:

(a-2-1) amplifying said first degenerate DW-ACP extension product using said first target-specific primer to hybridize with a target-specific nucleotide sequence substantially complementary to a site on said known nucleotide sequence, whereby a

target-specific primer extension product is generated (in the amplification mix only the arbitrary primer=DW-ACP and first target specific primer and the first degenerate DW-ACP extension product produced at end of first stage amplification is present. At the second high stringency annealing temperature range of 50-60^{0}C taught by Stone & Wharton, the arbitrary primer=DW-ACP ceases to function as primer now only the first target specific primer anneals to said first degenerate DW-ACP extension product using said first target-specific primer to hybridize with a target-specific nucleotide sequence substantially complementary to a site on said known nucleotide sequence, whereby a target-specific primer extension product is generated),

Regarding claim 1, Stone & Wharton as evidenced by Welsh and McClelland do not teach:

(a-2-2) amplifying said target-specific primer extension product using a second DW-ACP to hybridize with a nucleotide sequence complementary to said first degenerate DW-ACP sequence of said target-specific primer extension product, whereby a second DW-ACP extension product is generated, and

(a-2-3) amplifying said second DW-ACP extension product using said second DW-ACP and said first target-specific primer, whereby a primary amplification product without a degenerate random nucleotide sequence is generated;

Regarding claim 1, Brenner (see whole section on rolling primers col 7-col. 11) teaches

(a-2-2) amplifying said target-specific primer extension product using a second DW-ACP (Brenner teaches use of complexity reducing nucleotides in the primers for

use in primer walking approach) see col. 7 lines 1-4. Thus by teaching use primer set containing complexity reducing nucleotides Brenner teaches a second DW-ACP) to hybridize with a nucleotide sequence complementary to said first degenerate DW-ACP sequence of said target-specific primer extension product, whereby a second DW-ACP extension product is generated (see col. 7 section rolling primers. Col. 8 lines 45-53 where sequences of the DW-ACPs called rolling primers is shown), and

(a-2-3) amplifying said second DW-ACP extension product using said second DW-ACP and said first target-specific primer, whereby a primary amplification product without a degenerate random nucleotide sequence is generated. (see col. 9 lines 9-58 where the process is taught how using primers P1 and P2 a primary amplification product without a degenerate random nucleotide sequence is generated).

Regarding claim 2, Welsh and McClelland teaches wherein said first-stage amplification is performed for one cycle (see page 7214 par. 1 where two cycle of primer annealing, primer extending and denaturing are taught. Thus teaching wherein said first-stage amplification is performed for one cycle).

Regarding claim 3, Welsh and McClelland teaches wherein said second-stage amplification is performed for at least 5 cycles (see page 7214 par. 1 where 10 cycles of high stringency second-stage amplification is taught. Thus teaching wherein said second-stage amplification is performed for at least 5 cycles).

Regarding claim 4, Stone and Wharton teaches wherein said first annealing temperature is between about 35°C and 50°C (see page 2613 par. 1 where range of

first annealing temperature from about 40°C to 50°C is taught. Thus Stone and Wharton teaches said first annealing temperature is between about 35°C and 50°C).

Regarding claim 5, Stone and Wharton teaches wherein said second annealing temperature is between about 50°C and 72°C (see page 2613 par. 1 where annealing temperature is between 50°C to 60°C is taught. Thus Stone and Wharton teach wherein said second annealing temperature is between about 50°C and 72°C).

Regarding claim 13, Stone & Wharton teaches wherein said nucleotide sequence to be amplified is gDNA or cDNA (see page 17 line 1 where nucleotide sequence to be amplified is taught to be gDNA or cDNA).

Regarding claim 18, Stone and Walker teaches wherein p represents an integer of 10 to 60 (see list of arbitrary primers in table 1C on page 2613. The 5' end of the primer CE NheI shows p represents an integer of 12 thus teaching wherein p represents an integer of 10 to 60).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Brenner in the method of Stone & Wharton as evidenced by Welsh and McClelland. The motivation to do so is provided to one of ordinary skill in the art by teachings of Brenner.

Stone & Wharton as evidenced by Welsh and McClelland teach a method for amplifying an unknown nucleotide sequence adjacent to a known nucleotide sequence. These amplified fragments were run on gel to identify how many different regions were amplified, then the DNA was extracted from gel slices before it was reamplified, cloned

into plasmids before the sequencing could be performed to identify DNA sequence of the unknown nucleotide sequence (see page 2613 par. 2-4 of methods section).

Brenner teaches a method of using rolling primers (see col. 9- col. 12, the entire section dealing with sequencing) where the amplified products can be directly sequenced without requiring the separation of the amplified products on gels their re extraction from gel slices, re amplification and cloning into plasmids. Thus one of ordinary skill in the art realizes the advantages provided by practicing the method of Brenner in the method of Stone & Wharton as evidenced by Welsh and McClelland in terms of ease of performance, arriving at a method that requires less manipulation and is thus also more efficient.

Thus the method Stone & Wharton as evidenced by Welsh and McClelland amplifies an unknown nucleotide sequence adjacent to a known nucleotide sequence and the method of Brenner allows unambiguous identification of the DNA sequence of this unknown nucleotide sequence because in the method of Brenner "the primers "roll" along the polynucleotide during the sequencing process, moving a base at a time along the template with each cycle" (see last part of abstract).

Regarding claim 1 neither Stone & Wharton as evidenced by Welsh & McClelland nor Brenner teach

wherein said first degenerate DW-ACP has a general formula I:

$5'\text{-}X_p\text{-}Y_q\text{-}Z_r\text{-}Q_s\text{-}3'$ (I)

wherein, X_p represents a 5'-end portion having a pre-selected nucleotide sequence,

Y_q represents a regulator portion comprising at least two contiguous universal base or non- discriminatory base analog residues,

Z_r represents a degenerate random sequence portion having a degenerated random nucleotide sequence,

Q_s represents a 3'-end portion having a hybridizing nucleotide sequence substantially complementary to a site on said unknown nucleotide sequence to hybridize therewith, p, q, r, and s represent the number of nucleotides, and X, Y, Z, and Q are deoxyribonucleotide or ribonucleotide.

Regarding claim 1, Chun teaches wherein said first degenerate DW-ACP has a general formula I:

5'-X_p-Y_q- Z_r-Q_s-3' (I)

wherein, X_p represents a 5'-end portion having a pre-selected nucleotide sequence,

Y_q represents a regulator portion comprising at least two contiguous universal base or non- discriminatory base analog residues,

Z_r represents a degenerate random sequence portion having a degenerated random nucleotide sequence,

Q_s represents a 3'-end portion having a hybridizing nucleotide sequence substantially complementary to a site on said unknown nucleotide sequence to hybridize therewith, p, q, r, and s represent the number of nucleotides, and X, Y, Z, and Q are deoxyribonucleotide or ribonucleotide.

(See Fig. 5 of the WO document where nucleic acid containing all the above shown in step 3 as 5' oligo that is used after RT using 3' primer).

Regarding claim 7, Chun teaches wherein said regulator portion in said first degenerate DW-ACP is capable of restricting the annealing portion of said primer to its 3'-end portion at said first annealing temperature (See page 144, claim 79).

Regarding claims 14-16, Chun teaches wherein said universal base or non-discriminatory base analog residue is deoxyinosine (see page 19 line 21, also see page 20, line 21)

Regarding claims 19-20, Chun teaches wherein q is at least 3 (claim 19) or wherein q represents an integer of 2 to 10 (see page 20 lines 6-8 where at least 3 universal bases as well as primer containing 2-5 universal bases is taught).

Regarding claim 21, Chun teaches wherein r represents an integer of 2 to 5 (see page104 line 30 where SEQ ID NO 83 is taught. In this JYC2-HD1 primer the sequence following 5 Inosine, GT represents the Z_r and here r represents an integer of 2 to 5. The sequence NCRR is 4).

Regarding claim 22, Chun teaches wherein s represents an integer of 3 to 10 (see page104 line 30 where SEQ ID NO 83 is taught. In this JYC2-HD1 primer the sequence at 3' end following NCRR is 8 nt long shown as --GTGTGGTT-3'. Thus teaching wherein s represents an integer of 3 to 10).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Chun in the method of Stone & Wharton as evidenced by Welsh & McClelland and Brenner. The motivation to do so is

provided to one of ordinary skill by teaching of Chun who state in the section entitled "Example 9: Identification of conserved homology segments in multigene families using ACP. The ACP of the subject invention was applied to detect and clone conserved homology segments in multigene families. In the present example, degenerate primers were designed to detect homeobox sequences.---- The following ACPs comprise the degenerate sequences for homeobox sequences at their 3' end portions and were used as degenerate homeobox -specific primers for the first-stage PCR amplification". (See page 104 lines 18-29). They go on to state on page 105 lines 29-32 and page 106 lines 1-2 "These results indicate that the method using the ACP of the present invention for isolating conserved homology segments in multigene families produces only real PCR products. Freedom from false positives, which is a major bottleneck remaining in the previous PCR-based techniques for isolating conserved homology segments in multigene families, allows avoiding the subsequent labor intensive work required for the verification of the amplified cDNA fragments."

Thus based on this explicit teaching of Chun one of ordinary skill in the art is motivated to use the principles employed by Chun to design the primers to use in the method of Stone & Wharton as evidenced by Welsh & McClelland and Brenner and have a reasonable expectation of success in being able to identify conserved homology segments in multigene families using such primers without performing labor intensive work required for the verification of the amplified cDNA fragments.

8. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stone & Wharton as evidenced by Welsh & McClelland; Brenner in view of Chun as

applied to claim 1 above, and further in view of Liu and Whittier (1995) Genomics 25, 674-681 (previously cited); Watanabe et al. 2001 Journal of Microbiological methods 44 : pp 253-262 (previously cited); and Oberste et al. J Clin. Microbiol. Vol. 37 no 5 May 1999 pp. 1288-1293 (previously cited).

Regarding claim 9, Stone & Wharton as evidenced by Welsh & McClelland; and Brenner in view of Chun teach method of claim 1 above. But they do not teach wherein said method further comprises the step of (c) performing a secondary amplification at a third annealing temperature, comprising at least one cycle of primer annealing, primer extending and denaturing, using a third DW-ACP comprising at its 3'-end portion a nucleotide sequence to hybridize with the opposite-sense nucleotide sequence to said second DW-ACP sequence present at the 3'-end of said primary amplification product and said first target-specific primer of the step (a) or a nested target- specific primer designed to amplify an internal region of said primary amplification product.

Regarding claim 9, Liu and Whittier teaches wherein said method further comprises the step of (c) performing a secondary amplification at a third annealing temperature, comprising a nested target-specific primer designed to amplify an internal region of said primary amplification product. (see page 676 fig. 1 where internal primers SP2 and SP3 are taught for nested PCR referred to as secondary and tertiary PCR in bottom of fig. 1. Thus teaching a nested target-specific primer designed to amplify an internal region of said primary amplification product).

Regarding claim 10, Liu and Whittier teaches annealing temperature is between about 50°C and 72°C (see page 680 par. 2 where guidelines are provided as to how to

set annealing temperatures for high stringency conditions. They teach tm's of the specific primers should be at least 10^0C higher than the average tm's of the AD primers, and the annealing temperatures in the high–stringency cycles should be set as high as possible (usually 1-5^0C higher than the calculated specific primers). In the instant case the tm of the AD3 and AD4 primers is 47-48^0C see page 675 par. 3 . So using the guidelines the tm of the specific primers SP2 and SP3 used for nested PCR in this case has to be 57-58^0C. So the third temperature condition for performing high stringency annealing temperature for nested PCR should be at least 1-5^0C higher than the calculated specific primers tm which will be 58-63^0C. Thus by teaching annealing temperature of 58-63^0C, Liu and Whittier teaches annealing temperature is between about 50°C and 72°C).

Regarding claim 11, Liu and Whittier teaches performing nested PCR where a small aliquot of the amplified product is diluted and used as a template for nested PCR (see page 675 last part of par. 2 in per procedure where secondary and tertiary (nested PCR) PCRs are taught. It would have been prima facie obvious to one of ordinary skill in the art wherein said method further comprises the step (b) of purifying a reaction resultant of the step (a) to remove said first degenerate DW-ACP, said second DW-ACP and said first target-specific primer prior to performing the step (c). One of ordinary skill in the art performs nested PCR to quantify or for un ambiguous detection of the amplified region. Hence the purpose of performing the nested PCR in step C is to obtain specific amplified product with a reasonable yield for further use. During classic nested PCR simply a dilution of the amplified product is done and to this diluted sample, PCR

primers needed for nested PCR are added. That means the mixture on which nested PCR is being performed may still contains some of the original template and degenerate primer/first specific target primers. Therefore by performing the purification of the amplified product all primers used in the previous amplification are removed. Thus this purified product can be used as a template for nested PCR with no possibility of interference from the previously used PCR primers. Purification of PCR product prior to performing nested PCR will ensure that only the PCR product that was amplified initially using degenerate primer and target specific primer is amplified further. There will be no carry over of the primers used initially that can generate spurious background or amplification of some other regions primed by annealing of the degenerate primers on the original template that will still be present if only a dilution was performed as is routine in nested PCRs.

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of Liu and Whittier in the method of Stone & Wharton as evidenced by Welsh & McClelland; in view of Brenner and further in view of Chun at the time the invention was made. The motivation to do so is provided by both Watanabe et al. and Oberste et al.

Stone & Wharton as evidenced by Welsh & McClelland; Brenner; and Chun teach a method for amplifying an unknown nucleotide sequence adjacent to a known nucleotide sequence. The method is also referred to as genome fingerprinting in the art. Method of Stone & Wharton as evidenced by Welsh & McClelland; Brenner and Chun do not teach use of nested PCR in genome fingerprinting. Liu and Whittier teach two

arbitrary primers that contain universal or non-discriminatory in the regulator portion of the arbitrary primers. These primers also have the right melting temperatures that would meet the annealing temperature range requirements of the instant method. Motivation to use the inosine containing arbitrary primers of Liu and Whittier to perform nested PCR in the method of Stone & Wharton as evidenced by Welsh & McClelland; Brenner and Chun is provided to one of ordinary skill in the art at the time the invention was made by state of the art at that time. A survey of the literature published in the fingerprinting field tells one of ordinary skill that artisans practicing in the field of fingerprinting have successfully introduced inosines in the universal primers used for amplifying 16S ribosomal DNA from a community of bacteria. These inosine containing degenerate primers were able to reduce amplification biases caused by mismatches that were observed using unmodified universal primers. (see abstract Watanabe et al. 2001). Oberste et al. 1999 designed primers to amplify unknown Enteroviruses (EVs). These primers were designed with inosines to account for the differences between different virus groups and for codon degeneracy (the inosine containing primers are shown in Table 1 page 1289 of Oberste et al. 1999). Using this set of inosine containing degenerate primers they were able to amplify 51 EV strains isolated from clinical material between 1991 and 1998. Art taught that there is high degree of genetic diversity among the EVs and therefore posed a challenge in the systematic design of nucleic acid based diagnostic reagents (see page 1292 par. 2 of discussion). Oberste et al. go on to state "Degenerate inosine containing PCR primers were developed to overcome such nucleotide sequence diversity by specifically targeting regions of

conserved amino acid sequences". (see page 1292 last part of par. 2 under discussion). Therefore inosine containing primers have been used by one of ordinary skill in the art for performing fingerprinting.

These teachings of Watanabe et al.; and Oberste et al. teach one of ordinary skill that by using the degenerate primers containing inosines taught by Liu and Whittier in the method of Stone & Wharton as evidenced by Welsh & McClelland; Brenner and Chun they have a reasonable expectation of success in not only being able to successfully perform fingerprinting analysis from diverse unknown bacterial or viral clinical isolates but also accurately determine the nucleic acid sequence of the identified organism.

Conclusion

9. Thus all claims under consideration 1-5, 7-16 and 18-22 are rejected over prior art.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
July 21, 2009